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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 12292003

Application Number: 09/529,762
Filing Date: April 18, 2000
Appellant(s): RITTERSHAUS ET AL.

David G. O'Brien
Leon R. Yankwich
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 10/14/03

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The appellant's Brief includes statements that
As to issue 1, claims 40-48 and 51-52 stand or fall together,
As to issue 2, claims 40-48 and 51-52 stand or fall together,
As to issue 3, claims 40, 41, 42, 43, 44 and 45 recites a separate element that is not taught by Kwoh, and thus each claim is separately patentable in view of Kwoh. Claims 46, 48, 51 and 53 are multiple dependent from any of claims 40-45 and will stand or fall together on the patentability of the base claims.
The appellant's statement regarding issue 3 in the brief that certain claims do not stand or fall together is not agreed with because of the following reasons. Claim 41 is related to claim 40 because achieving a level of essentially 0 μg if CETP per ml (claim 41) would reduce the CETP activity (claim 40) to below 20% of that of untreated mammal. Further, the increase in

circulating HDL (claims 42-43) and the decrease in circulating LDL (claim 44-45) are functionally related to the activity of CETP. As stated in the summary of the invention (page 3 of the brief), CETP mediates transfer of HDL to VLDL and LDL and also the reciprocal exchange of VLDL to HDL. High CETP activity has been correlates with decreased levels of HDL and increased levels of LDL. The inhibition of CETP activity by injection of non-endogenous CETP to generate autoantibodies to CETP (claimed invention), thereby blocking the function of CETP, would expected to reverse the HDL and LDL levels. Thus claims 40-45, 47 and 51-52 should stand or fall together.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

WO 96/39168	WIPO	12-12-1996

Stevens et al, in Synthetic Vaccines Vol. II, chapter 18, pages 111-133, 1987.

Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495.

Kuby et al., 1994, in Immunology Second edition, W H Freeman and Company, NY, pp. 85-94.

Marrott *et al* (PTO 1449), NATURE, VOL 364, pages 73-75, JULY 1993

Breslow *et al* (PTO 1449), Proc. Natl. Acad. Sci. USA Vol. 90, pp. 8314-4318, September 1993

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejection - 35 USC § 112, first paragraph Enablement

Claims 40-48 and 51-52 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method of increasing the production of anti-CETP antibody wherein the method comprises administering to a rabbit a C-terminus of human CETP peptide conjugated to tetanus toxoid consisting of SEQ ID NO: 7 or a whole recombinant

human CETP consisting of SEQ ID NO: 1 (See page 17 lines 2-3 of the specification) for reducing CETP activity, increasing the HDL-cholesterol, and lowering LDL-cholesterol associated with atherosclerosis, **does not** reasonably provide enablement for (1) a method of modulating the level of endogenous, active cholesteryl ester transfer protein (CETP) in *any* mammal comprising administering to the mammal *any* whole, non-endogenous CETP in an amount effective to reduce CETP activity below 20% of that the untreated mammal, (2) a method of modulating the level of endogenous cholesteryl ester transfer protein (CETP) in a mammal comprising administering to the mammal *any* whole, non-endogenous CETP in an amount effective to achieve a level of essentially 0 μg of CETP per milliliter of blood of the mammal, (3) a method of modulating the level of HDL-cholesterol in a mammal comprising administering to the mammal *any* whole, non-endogenous CETP in an amount effective to achieve a lipoprotein profile wherein greater than about 90% of the total cholesterol in the blood of the mammal is HDL-cholesterol, (4) the method of modulating the level of HDL-cholesterol in a mammal comprising administering to the mammal *any* whole, non-endogenous CETP in an amount effective to achieve a lipoprotein profile wherein greater than about 100% of the total cholesterol in the blood of the mammal is HDL-cholesterol, (5) a method of modulating the level of LDL-cholesterol in a mammal comprising administering to the mammal *any* whole, non-endogenous CETP in an amount effective to achieve a lipoprotein profile wherein less than about 10% of the total cholesterol in the blood of the mammal is LDL-cholesterol, (6) a method of modulating the level of LDL-cholesterol in a mammal comprising administering to the mammal *any* whole, non-endogenous CETP in an amount effective to achieve a lipoprotein profile wherein essentially none of the total cholesterol in the blood of the mammal is LDL-cholesterol, (7) the method wherein the mammal is a human, (8) the method wherein *any* whole, non-endogenous cholesteryl ester transfer protein is any xenogeneic CETP, *any* allelic variant of *any* mammalian's endogenous CETP, *any* mammalianized non-endogenous CETP in which the amino acid sequence of a non-endogenous CETP ahs been altered by deletion or substitution of one or more amino acids so as to make the amino acid sequence of said non-endogenous CETP more similar to the mammal's endogenous CETP, (9) *any* method mentioned above in combination with an adjuvant such as the ones recited in claim 52 for non-specifically stimulate the immune response of the mammal for a vaccine against LDL-cholesterol. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a full-length rabbit CETP polypeptide consisting of SEQ ID NO: 3, a full-length human CETP polypeptide consisting of SEQ ID NO: 1, two mammalianized rabbit CETP polypeptides consisting of SEQ ID NOS: 5 and 6 and a method of vaccinating a rabbit, which is a mammal, with a recombinant human CETP of SEQ ID NO: 1, or a peptide of the C-terminus of human CETP conjugated to tetanus toxoid of SEQ ID NO: 7 (See page 16-17, Figs 8-9 of the specification) for increasing the titer of CETP specific antibodies in the plasma, wherein said antibody cross-react with the rabbit CETP c-terminal peptide from amino acids 477-496 of SEQ ID NO: 3, thereby reducing the CETP activity below 20% of the untreated control at 14 weeks (Fig 9), reducing the level of native CETP to 0 μg/ml of blood of the mammal at 14 weeks post immunization, increasing the level of HDL-cholesterol to greater than 90% of the total cholesterol in the blood of the mammal, increasing the level of HDL-cholesterol to about 100% of the total cholesterol in the blood of the mammal 14 weeks after immunization (Fig 9), reducing the level of LDL-cholesterol of less than about 10% of the total cholesterol in the blood plasma of the mammal (See Fig 7). The specification further discloses on page 5 line 23 that non-endogenous CETP can be from another mammalian species such as rabbit CETP, mouse CETP or simian CETP for administration to a human.

Other than the specific polypeptides mentioned above for a method of inhibiting the endogenous CETP activity, the specification fails to provide any guidance as how to make and use *any* non-endogenous CETP for a method of modulating any endogenous CETP in any mammal. There is insufficient guidance and working examples as to which amino acid residues within any of the non-endogenous CETP of any mammal can be deleted, substitute and whether the resulting modified CETP protein would maintain the structure and function as SEQ ID NO: 7 and 1, in turn, generating antibodies that would bind specifically to the human or the rabbit CETP for a method of inhibiting any endogenous CETP activity associated with atherosclerosis. Given

the indefinite number of undisclosed non-endogenous CETP protein, it is unpredictable which undisclosed non-endogenous CETP would be useful for a method of inhibiting any non-endogenous CETP activity associated with atherosclerosis.

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (see Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

It is well known in the art at the time the invention was made that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimentional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization with a peptide comprising a contiguous amino acid sequence of 8 amino acid residues or a protein derived from a full-length polypeptide may result in **antibody specificity** that differs from antibody specificity directed against the native full-length polypeptide. Without the specific amino acid residues, it is unpredictable to determine which antibody response generated from any CETP polypeptide and fragment thereof will have the same antibody specificity as an antibody generated from the SEQ ID NO: 1 and 7, in turn, can be use for a method of reducing CETP activity associated with atherosclerosis.

Furthermore, Marrott *et al* (PTO 1449) teach that transgenic mice expressing exogenous simian cholesteryl ester transfer protein (CETP) results in severe atherosclerosis with a marked increases in the concentration of LDL-cholesterol and a decrease in the concentration of HDL-cholesterol (See entire document, Abstract, in particular). Likewise, Breslow *et al* (PTO 1449) teach human CETP transgenic mice overexpressing human CETP has lower level of HDL-cholesterol the effects CETP were less than expected based on studies comparing normal and CETP-deficient humans (See page 8316, column 2, CETP transgenic mice, in particular). These results indicate that not all xenogeneic none-endogenous CETP are appropriate for a method of modulating CETP activity, particularly in humans, where atherosclerosis is multi-factorial complex disease.

With regard to allelic variant of *any* mammal's endogenous CETP, the specification defines allelic variant is a polymorphism of human CETP producing by another human individual (See page 8, lines 20 of the specification). However, the specification discloses only **one** human CETP polypeptide consisting of SEQ ID NO: 1. There are no additional human CETP which have been demonstrate to be useful for immunizing any mammal, in turn, for a method of

modulating any endogenous CETP within any mammal. Given the indefinite number of undisclosed non-endogenous CETP protein, it is unpredictable which undisclosed non-endogenous CETP would be useful for a method of inhibiting any non-endogenous CETP activity associated with atherosclerosis. It follows that any xenogeneic CETP, any allelic variant of any mammalian's endogenous CETP, any mammalianized non-endogenous CETP other than SEQ ID NO: 5 and 6 are not enable.

Regarding claims 46 and 48 wherein the mammal is a human, there are no working examples in the specification as filed to demonstrate that administering any whole non-endogenous CETP such as recombinant human CETP is effective in reducing CETP activity below 20% of that untreated human, reducing the level of essentially 0 μg of CETP per ml of blood of the human, increasing the level of HDL-cholesterol to greater than about 90% or about 100% of the total cholesterol in the blood of the human, lowering the level of LDL-cholesterol to less than 10% of the total cholesterol in the blood plasma or reducing the level of LDL-cholesterol to essentially none as recited in claim 45. Furthermore, since CETP is a "self" protein, it is not clear in the specification as filed how administering a whole recombinant human CETP (which is not foreign and no different than one's own CETP) would induce endogenous **antibody** direct toward one's own CETP at a level **sufficient high** to modulate one's own level of endogenous CETP activity. Stevens *et al* teach in order induce high levels of antibodies reactive to one's own protein (break immune tolerance) such as hCG for a contraceptive vaccine, the protein must be conjugated to a foreign protein or carrier molecule such as KLH or tetanus toxoid to enhance the immunogenicity of the hCG protein. In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Claim Rejection - 35 USC § 112, first paragraph Written Description

Claims 40-48 and 51-52 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) a method of modulating the level of endogenous, active cholesteryl ester transfer protein (CETP) in *any* mammal comprising administering to the mammal *any* whole, non-endogenous CETP in an amount effective to reduce CETP activity below 20% of that the untreated mammal, (2) a method of modulating the level of endogenous cholesteryl ester transfer protein (CETP) in a mammal comprising administering to the mammal *any* whole, non-endogenous CETP in an amount effective to achieve a level of essentially 0 μg of CETP per milliliter of blood of the mammal, (3) a method of modulating the level of HDL-cholesterol in a mammal comprising administering to the mammal *any* whole, non-endogenous CETP in an amount effective to achieve a lipoprotein profile wherein greater than about 90% of the total cholesterol in the blood of the mammal is HDL-cholesterol, (4) the method of modulating the level of HDL-cholesterol in a mammal comprising administering to the mammal *any* whole, non-endogenous CETP in an amount effective to achieve a lipoprotein profile wherein greater than about 100% of the total cholesterol in the blood of the mammal is HDL-cholesterol, (5) a method of modulating the level of LDL-cholesterol in a mammal comprising administering to the mammal *any* whole, non-endogenous CETP in an amount effective to achieve a lipoprotein profile wherein less than about 10% of the total cholesterol in the blood of the mammal is LDL-cholesterol, (6) a method of modulating the level of LDL-cholesterol in a mammal comprising administering to the mammal *any* whole, non-endogenous CETP in an amount effective to achieve a lipoprotein profile wherein essentially none of the total cholesterol in the blood of the mammal is LDL-cholesterol, (7) the method wherein the mammal is a human, (8) the method wherein *any* whole, non-endogenous cholesteryl ester transfer protein is any xenogeneic CETP, *any* allelic variant of *any* mammalian's endogenous CETP, *any* mammalianized non-endogenous CETP in which the amino acid sequence of a non-endogenous CETP ahs been altered by deletion or substitution of one or more amino acids so as to make the amino acid sequence of said non-endogenous CETP more similar to the mammal's endogenous CETP, (9) any method mentioned above in combination with an adjuvant such as the ones recited in claim 52 for non-specifically stimulate the immune response of the mammal for a vaccine against LDL-cholesterol.

The specification discloses only a full-length rabbit CETP polypeptide consisting of SEQ ID NO: 3, a full-length human CETP polypeptide consisting of SEQ ID NO: 1, a mammalianized rabbit CETP consisting of SEQ ID NOS: 5 and 6 and a method of vaccinating a rabbit, which is a mammal, with a recombinant human CETP of SEQ ID NO: 1, or a peptide of the C-terminus of

human CETP conjugated to tetanus toxoid of SEQ ID NO: 7 (See page 16-17, Figs 8-9 of the specification) for increasing the titer of CETP specific antibodies in the plasma, wherein said antibody cross-react with the rabbit CETP c-terminal peptide from amino acids 477-496 of SEQ ID NO: 3, thereby reducing the CETP activity below 20% of the untreated control at 14 weeks (Fig 9), reducing the level of native CETP to 0 μg/ml of blood of the mammal at 14 weeks post immunization, increasing the level of HDL-cholesterol to greater than 90% of the total cholesterol in the blood of the mammal, increasing the level of HDL-cholesterol to about 100% of the total cholesterol in the blood of the mammal 14 weeks after immunization (Fig 9), reducing the level of LDL-cholesterol of less than about 10% of the total cholesterol in the blood plasma of the mammal (See Fig 7).

With the exception of the specific CETP polypeptides mentioned above, there is insufficient written description about the structure associated with functions of *any* non-endogenous CETP wherein said endogenous CETP is *any* xenogeneic CETP, *any* allelic variant of any mammalian's endogenous CETP, *any* mammalianized non-endogenous CETP having one more amino acid altered by deletion, or substitution as to make the amino acid sequence more similar to the mammal's endogenous CETP for a method of modulating the level of endogenous active cholesteryl ester transfer protein associated with atherosclerosis.

Given the lack of a written description of *any* additional representative species of allelic variant of *any* human CETP such as any naturally occurring polymorphism as encompassed by the claims, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Claim Rejection - 35 USC § 102 (a)

Claims 40-45, 47 and 51-52 stand rejected under 35 U.S.C. 102(a) as being anticipated by the WO 96/39168 publication (Dec 12, 1996, PTO 892).

The 96/39168 publication teaches a method of modulating the endogenous active cholesteryl ester transfer protein (CETP) in a mammal such as a rabbit comprising administering to said mammal a full-length human CETP of SEQ ID NO: 1 of WO 96/39168, or a taxoid conjugated human CETP peptide, which are non-endogenous CETP, in an amount effective to stimulate an immune response such as anti-CETP antibody wherein said antibody inhibits the function of CETP such as reducing the CETP activity as compared to that of the untreated mammal (See abstract, summary of invention, claim 2 of WO96/39168, in particular). The reference further teaches administering a non-endogenous CETP that has been altered by deletion such as a CETP peptide of SEQ ID NO: 3 that is taken from human and made similar to the rabbit's endogenous CETP (See abstract, Fig 2, page 7, lines 20, of WO 96/39168, in particular). The reference method comprises administered to the reference mammal such as rabbit the reference non-endogenous CETP in combination with an adjuvant such as CFA (Complete Freund's Adjuvant) or IFA (Incomplete Freund's adjuvant) wherein the reference adjuvant is effective to non-specifically stimulate the immune response of the mammal such as production of antibody (See page 7, line 29, page 8, lines 1-2, in particular). The reference method reduces the risk of atherosclerosis by raising the HDL cholesterol level (See abstract, page 14, lines 24-30, in particular), decreases CETP activity (Figure 2, page 10, lines 1-4, in particular). The reference method decreases LDL-cholesterol to less than 16% of the total cholesterol in the serum (blood plasma), which is about 10% (See Table 1, page 11, in particular). The term "about" expands the claimed 10% of the total cholesterol to read on the reference 16%. Claim 47 is included in this rejection because the reference teaches xenogeneic CETP which is a human CETP, in addition to a mammalianized non-endogenous CETP (See SEQ ID NO: 3 of WO 96/39168) where the reference SEQ ID NO: 3 is common to both human and rabbit CETP, which makes the human CETP more similar to rabbit and vice versa (See page 7, lines 20-22, in particular).

While the reference is silent that the reference method reduces CETP activity below 20% of that of the untreated mammal, reduces the CETP level to essentially 0 ug of CETP per milliliter of blood of the mammal, increases the HDL-cholesterol level greater than about 90% to about 100% and reduces the LDL-cholesterol level to less than 10% of the total cholesterol, the reference method inherently would achieve the same results given that the reference non-

endogenous CETP (abstract, summary of invention and claim 2 of WO 96/39168 publication) is the same as that of the claimed non-endogenous CETP; the reference mammal such as the New Zealand white rabbit is the same mammal as disclsoed on page 16 lines 30 of instant application; the reference method steps such as the animals were boosted twice at one month intervals is the same as instant application (see page 17, line 15-16 of instant specification). The autoantibody generated from the same non-endogenous CETP in the mammal inherently has the same functions, such as increasing HDL cholesterol, decreasing CETP activity as taught by the WO96/39168 publication. Therefore the claimed method appears to be the same as the prior art method. Since the Patent Office does not have the facilities for examining and comparing the method of the instant invention to those of the prior art, the burden is on applicant to show that the prior art method is different from the claimed method. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977). Thus, the reference teachings anticipate the claimed invention.

(11) Response to Argument

Claim rejection - 35 U.S.C. § 112, first paragraph Enablement

At page 9 of the Brief, Appellants assert that the teaching of the specification satisfies the requirement under 35 U.S.C. § 112, first paragraph and entitle to a broader scope of the subject matter which Appellants are entitled to claim. Appellants argue that by Examiner's standard, the teaching could not be expanded to any other mammalian subject using any other whole non-endogenous CETP not having the exact same sequence as SEQ ID NO: 1.

Appellant's arguments have been fully considered but are not found to be persuasive. The term "non-endogenous CETP" as defined on page 5 of the specification can be CETP of another mammalian species (xenogeneic CETP), such as rabbit CETP, mouse CETP or simian CETP, allelic variation or polymorph of a mammalian CETP administered to the same species of mammal (e.g., a human CETP polymorph administered to another human; or the non-endogenous CETP can be a CETP from one species modified to have an amino acid sequence more similar to the native CETP of another species (e.g., a "humanized" rabbit CETP for administration to a human. The specification discloses only one full-length rabbit CETP polypeptide consisting of SEQ ID NO: 3, a full-length human CETP polypeptide consisting of SEQ ID NO: 1, a mammalianized rabbit CETP consisting of SEQ ID NOS: 5 and 6 for immunizing a rabbit for the claimed method.

Other than the specific CETP for the claimed method, there is insufficient guidance such as the amino acid sequence for other undisclosed "whole non-endogenous CETP" and whether administering said undisclosed non-endogenous (non-self) CETP would generate antibody against self (endogenous) CETP, or autoantibodies to endogenous (self) CETP, in turn, the autoantibodies would modulate the level of endogenous cholesteryl ester transfer protein such as reducing CETP activity below 20% of that untreated mammal (claim 40), achieving essentially 0 μg of CETP per ml of blood of the mammal (claim 41), achieving greater than about 90% or 100% of HDL-cholesterol (good cholesterol) as recited in claims (42-43) or reducing less than 10% of the LDL-cholesterol (bad cholesterol) in claim 44.

The specification fails to provide guidance as how to make any non-endogenous CETP, any xenogeneic CETP, any allelic variant of any mammalian' endogenous CETP, any non-endogenous CETP in which the amino acid sequence has been altered, such as which amino acid residues within any of the non-endogenous CETP of any mammal can be deleted, substitute and whether the resulting modified non-endogenous CETP protein would maintain the structure and function as SEQ ID NO: 7 and 1, in turn, generating antibodies that would bind specifically to self or endogenous CETP, in turn, the autoantibodies would be useful for a method of inhibiting any endogenous CETP activity associated with atherosclerosis as set forth in claims 40-48, 51 and 52. There is insufficient guidance as to the structure of any non-endogenous CETP, *any* "xenogeneic CETP", any "allelic variant" of any mammalian' endogenous CETP, any "non-endogenous CETP in which the amino acid sequence has been altered", such as which amino acid residues within any of the non-endogenous CETP of any mammal can be deleted, substitute. It is known that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein. Not only the structure such as the amino acid sequence of any undisclosed non-endogenous CETP is not enabled, the specification does not provide any guidance as to what changes should be made or what structural features that could distinguish non-endogenous CETP from others in the genus. Ngo *et al,* of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (see Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). Further, Kuby et al, of record, teach that immunization with a peptide comprising a contiguous amino acid sequence of 8 amino acid residues or a protein derived from a full-length polypeptide may result

in **antibody specificity** that differs from antibody specificity directed against the native full-length polypeptide (See Kuby 1994, page 94, in particular). Given the indefinite number of undisclosed non-endogenous CETP and without the specific amino acid sequence for the whole non-endogenous CETP such as any xenogeneic CETP, any "allelic variant" of any mammalian' endogenous CETP, any "non-endogenous CETP in which the amino acid sequence has been altered by deletion, or substitution of one or more amino acids", it is unpredictable which undisclosed non-endogenous CETP would generate antibody such as autoantibodies that is specific for self or endogenous CETP, in turn, useful for the claimed method. Until the time when such non-endogenous CETP such as "allelic variant" of any mammalian", or "non-endogenous CETP in which the amino acid sequence has been altered by deletion, or substitution are identified, the disclosure is merely extending an invitation to the artisan to use the current invention as a starting point for further experimentation. See Brenner v. Manson, 383 U.S. 519, 535-36, 148 USPQ 689, 696 (1966), noting that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." A patent is therefore not a license to experiment. Therefore, one of ordinary skill in the art would not be able to determine, without undue experimentation, which undisclosed non-endogenous CETP mentioned above would generate autoantibody that still binds to endogenous CETP, in turn, useful for modulating the level of endogenous cholesteryl as encompassed by the claimed method. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

At page 10 of the Brief, Appellants argue that by the Examiner's standard of patentability, no inventor could ever obtain useful patent coverage in this field unless a working example of each and every possible embodiment of the invention was actually printed in the application.

In contrast to Appellants' assertion that the Examiner raises the bar for patentability, the Examiner follows the published guideline, which is also available at www.uspto.gov.

At page 11 of the Brief, Appellants argue that claims are directed to methods of using a whole, non-endogenous CETP to produce a particular, measurable anti-atherogenic condition of unexpected proportions. In particular, Appellants have discovered that administering a whole, non-endogenous CETP to a mammal will elicit production of antibodies that react with the mammal's own, endogenous CETP resulting in: an unexpectedly low level of circulating CETP molecules (essentially no detectable CETP per ml of blood plasma) or of CETP activity below 20% of the activity in an untreated mammal, or an unexpectedly high level of blood cholesterol in the form of "good cholesterol", i.e., HDL-cholesterol greater than 90%, and as high as 100%, or and expectedly low level of blood cholesterol in the form of "bad cholesterol", i.e., LDL-cholesterol less than 10%, and as low as, essentially, none. Examples of achieving such measurable results according to Appellants' claimed methods are provided in the specification, using a well known rabbit model for atherosclerosis (see, Example 1 beginning at p. 16, and Figure 9 (demonstrating the results outlined above) of the specification). In addition, when rabbits were switched to a high cholesterol (atherogenic) diet, rabbits vaccinated with a whole, non-endogenous CETP had a demonstrably lower incidence of atherosclerotic lesions (Figure 14).

Appellant's arguments have been fully considered but are not found to be persuasive. The specification discloses four vaccine preparations. Rabbits are divided into four groups. Group I (negative control) was injected irrelevant antigen human chorionic gonadotropin (hCG), Group II was injected with C terminus of human CETP peptide, Group III was injected with whole recombinant human CETP (rhuCETP) and Group IV was injected with whole recombinant human CETP conjugated with tetanus toxoid (paragraph bridging page 16 and 17). The specification on page 19, lines 13-17 discloses that plasma lipoprotein for the Group III rabbit #32 shows the most reduction in LDL-cholesterol level (Fig 7), decreasing CETP activity, decreasing mass and increasing HDL (Figure 9). However, it is noted that the data from Figures 3, 7, 8 and 9 are based from only one rabbit (n =1). Further, the HDL-cholesterol level of whole recombinant human CETP (rhuCETP) treated group is not significantly different from the control (HCG) (See standard deviation bar, Figure 6, page 19, lines 4-7, in particular). Likewise, the change in CETP activity of whole recombinant human CETP (rhuCETP) treated group (Figure 4) is not significant different from the control group (hCG). Therefore, it is not clear that the skilled artisan could predict the efficacy of the claimed method exemplified in the specification as encompassed by the claims.

At page 12 of the Brief, Appellants argue that the specification provide an in vivo working example that used the rabbit model for atherosclerosis, which is a known and relied on by persons skilled in this art for studying and developing methods of treating atherosclerosis. Testing and optimization for a particular mammalian species is not undue experimentation and is not required by the statute.

Appellant's arguments have been fully considered but are not found to be persuasive. The issue here is not whether rabbit model is useful for atherosclerosis. The issue here is whether the specification enables any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

The specification discloses only one full-length rabbit CETP polypeptide consisting of SEQ ID NO: 3, a full-length human CETP polypeptide consisting of SEQ ID NO: 1, a humanized rabbit CETP consisting of SEQ ID NOS: 5 and 6 for immunizing a rabbit for the claimed method. The specification further discloses four vaccine preparations. Rabbits are divided into four groups. Group I (negative control) was injected irrelevant antigen human chorionic gonadotropin (hCG), Group II was injected with C terminus of human CETP peptide, Group III is injected with whole recombinant human CETP (rhuCETP) and Group IV is injected with whole recombinant human CETP conjugated with tetanus toxoid (paragraph bridging page 16 and 17).

However, the specification does not teach how to make any non-endogenous CETP, any xenogeneic CETP, any allelic variant of any mammalian' endogenous CETP, any non-endogenous CETP in which the amino acid sequence has been altered, such as which amino acid residues within any of the non-endogenous CETP of any mammal can be deleted, substitute and whether the resulting modified non-endogenous CETP protein would maintain the structure and function as SEQ ID NO: 7 and 1, in turn, generating autoantibodies that would bind specifically to self or endogenous CETP, for a method of inhibiting any endogenous CETP activity associated with atherosclerosis as set forth in claims 40-48, 51 and 52. There is insufficient guidance as to the structure of any non-endogenous CETP, *any* "xenogeneic CETP", *any* "allelic variant" of *any* mammalian' endogenous CETP, any "non-endogenous CETP in which the amino acid sequence has been altered", such as which amino acid residues within any of the non-endogenous CETP of any mammal can be deleted, substitute. It is known that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein. Not only the structure such as the amino acid sequence of any undisclosed non-endogenous CETP is not enabled, the specification does not provide any

guidance as to what changes should be made or what structural features that could distinguish non-endogenous CETP from others in the genus. Ngo *et al,* of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (see Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). Further, Kuby et al, of record, teach that immunization with a peptide comprising a contiguous amino acid sequence of 8 amino acid residues or a protein derived from a full-length polypeptide may result in **antibody specificity** that differs from antibody specificity directed against the native full-length polypeptide (See Kuby 1994, page 94, in particular). Given the indefinite number of undisclosed non-endogenous CETP and without the specific amino acid sequence for the whole non-endogenous CETP such as xenogeneic CETP, "allelic variant" of any mammalian' endogenous CETP, and "non-endogenous CETP in which the amino acid sequence has been altered by deletion, or substitution of one or more amino acids", it is unpredictable which undisclosed non-endogenous CETP would generate antibody that is specific for self or endogenous CETP, in turn, useful for the claimed method. Until the time when such non-endogenous CETP mentioned above are identified, the disclosure is merely extending an invitation to the artisan to use the current invention as a starting point for further experimentation. Given the indefinite number of undisclosed non-endogenous CETP, there is insufficient working example demonstrating any undisclosed non-endogenous CETP is effective for generating autoantibodies that bind specifically to the endogenous mammalian CETP, let alone using the undisclosed non-endogenous CETP for lowing level of circulating CETP molecules (essentially no detectable CETP per ml of blood plasma) or of CETP activity below 20% of the activity in an untreated mammal, or raising the "good cholesterol", i.e., HDL-cholesterol greater than 90%, and as high as 100%, or/and lowing the "bad cholesterol", i.e., LDL-cholesterol less than 10%, and as low as, essentially, none in any mammal as encompassed by the claimed method.

At pages 13-14 of the Brief, Appellants argue that the claimed method does not reside in a particular non-endogenous CETP employed. Persons skilled in the art are assumed to already know how easily determine whether one CETP is the same or different from the endogenous CETP in a particular mammalian subject. Appellants assert that even if the source of a CETP molecule is unknown, determination of whether a mystery CETP molecule is non-endogenous to

a mammal to be treated is easily determined by those skilled in this art using no more than routine analytical procedures.

Appellant's arguments have been fully considered but are not found to be persuasive. Claim 47 still recites the method according to any of claims 40-45, wherein the whole, non-endogenous cholesteryl ester transfer protein (CETP) is selected from the group consisting of a xenogeneic CETP, an allelic variant of the mammalian's endogenous CETP; and a mammalianized, non-endogenous CETP in which the amino acid sequence of any non-endogenous CETP has been altered by deletion or substitution of one or more amino acids so as to make the amino acid sequence of said non-endogenous CETP more similar to the mammal's endogenous CETP. However, the specification does not define what is meant by more similar to the mammalian's endogenous CETP. Although the specification discloses two mammalianized rabbit CETP consisting of SEQ ID NOS: 5 and 6, there is no working example demonstrating said mammalianized CETP are effective for the claimed method. Even if the non-endogenous CETP is limited to human CETP using the known rabbit model for atherosclerosis for the claimed method, the results such as the HDL-cholesterol level (See standard deviation bar, Figure 6, page 19, lines 4-7, in particular) of whole recombinant human CETP (rhuCETP) treated group and the CETP activity (standard deviation bar of Figure 4) are not significantly different from the control (HCG). In fact, the data such as the total cholesterol as shown in Figure 5 indicate clearly that individual variation exists, perhaps due to properties of the autoantibody generated in the method. Further, it is known at the time the invention was made that even a single amino acid substitution outside the antigenic site can exert drastic effects on binding specificity of the antibody. Given the indefinite number of undisclosed non-endogenous CETP such as xenogeneic CETP, an allelic variant of the mammalian's endogenous CETP, an a mammalianized, non-endogenous CETP in which the amino acid sequence of any non-endogenous CETP has been altered by deletion or substitution of one or more amino acids, it is unpredictable which undisclosed non-endogenous CETP would generate autoantibody that binds specifically to the endogenous CETP, in turn, would effectively modulate the level of endogenous choleteryl ester transfer, HDL and LDL for the claimed method as set forth in claims 40-52.

At pages 15-16 of the Brief, Appellants argue that the Examiner focuses on what the present specification does or does not contain and not at all on the capability of persons skilled in the art. A patent specification does not teach, and preferably omits wheat is well known in the

art. What Appellants have disclosed is that whole non-endogenous CETP may be administered to a mammalian subject and result in endogenous CETP levels that are unexpectedly low, endogenous HDL levels that are unexpectedly high, and endogenous LDL levels that are unexpectedly low. Appellants submit that persons skilled in the art, seeing the operation of Appellants' method in this model, would believe that additional mammals and additional CETPs would operate in a like manner.

Appellant's arguments have been fully considered but are not found to be persuasive. The specification discloses only two whole non-endogenous CETP from rabbit (SEQ ID NO: 3) and human (SEQ ID NO: 1). The specification further discloses two humanized rabbit CETP consisting of SEQ ID NOS: 5 and 6 for immunizing a rabbit for the claimed method. Other than the specific whole, non-endogenous CETP mentioned above, the specification does not teach how to identify and/or make other non-endogenous CETP such as any non-endogenous CETP in which the amino acid sequence has been altered, such as which amino acid residues within any of the non-endogenous CETP of any mammal has been deleted, or substituted and whether the resulting modified non-endogenous CETP protein would maintain the structure and function as SEQ ID NO: 7 and 1, in turn, generating autoantibodies that would bind specifically to self, endogenous CETP, for a method of inhibiting any endogenous CETP activity associated with atherosclerosis as set forth in claims 40-48, 51 and 52. There is insufficient guidance as to the identity of the other "non-endogenous CETP", not to mentioned the binding specificity of the autoantibodies using the undisclosed "non-endogenous CETP and whether it is useful for the claimed method. Further, there is insufficient in vivo working example in the specification as filed demonstrating other mammalian CETP would operate in a like manner. In fact, the unexpectedly low endogenous CETP levels, and the unexpectedly high endogenous HDL levels are from one rabbit immunized with only whole non-endogenous human CETP.

Claim rejection - 35 U.S.C. § 112, first paragraph Written Description

At pages 17-19 of the Brief, Appellants argue that in the present application, there is an actually reduction to practice of treatment to reduce CETP activity, raise HDL above 90% to 100% and to lower LDL to less than 10% to essentially to none using a whole, non-endogenous CETP vaccine. The disclosure provides a written description for the complete amino acid structure for whole human and rabbit CETP (SEQ ID NOS: 1 and 3) and written description of methods for assaying the effectiveness of the vaccine. Appellants argue that the examiner

appears to require a written description of the use of every possible embodiment of whole, non-endogenous CETP to reduce CETP activity, raise HDL levels, or lower LDL levels in order to satisfy the written description requirement under 35 USC § 112, first paragraph.

Appellant's arguments have been fully considered but are not found to be persuasive. The claims are drawn to a method of modulating the level of endogenous cholesteryl ester transfer protein (CETP) activity using *any* mammalian whole none-endogenous CETP such as xenogeneic CETP, *any* allelic variant of any mammal's endogenous CETP, *any* mammalianized CETP that has been altered by deletion or substitution of one or more amino acids so as to make the amino acid sequence of said undisclosed non-endogenous CETP more similar to the undisclosed mammal's endogenous CETP. However, other than the specific CETP polypeptides mentioned above, there is insufficient written description about the structure associated with functions of *any* non-endogenous CETP wherein said endogenous CETP is *any* xenogeneic CETP, *any* allelic variant of any mammalian's endogenous CETP, *any* mammalianized non-endogenous CETP having one more amino acid altered by deletion, or substitution for a method of modulating the level of endogenous active cholesteryl ester transfer protein associated with atherosclerosis. Further, the specification discloses only two whole CETPs from human and rabbit (species), given the lack of a written description of *any* additional representative species of CETP such as the allelic variant of *any* human CETP, any naturally occurring polymorphism, any non-endogenous CETP that has been altered other than the humanized rabbit CETP as encompassed by the claims, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Claim rejection - 35 U.S.C. § 102(a)

At page 21 first paragraph of the Brief, Appellants argue that the example 2, Figure 2, and Table 1 of Kwoh describe a study in which rabbits were injected with a free, linear, toxoid-conjugated or non-conjugated 11-mer CETP fragment having a sequence in common with human and rabbit CETP. Thus unlike Appellant's invention, none of the rabbits in Kwoh was

administered a whole, non-endogenous CETP protein as is called for by each of the appealed claims.

Appellant's arguments have been fully considered but are not found to be persuasive. In contrast to Appellant's assertion that the reference does not teach administering a whole non-endogenous CETP, the 96/39168 publication teaches administering whole CETP non-endogenous CETP for the method as claimed (See abstract, summary of invention, claim 2 of WO96/39168 and SEQ ID NO: 1 of WO96/39168, in particular).

At page 21 second paragraph of the Brief, Appellants argue that Figure 2 of the Kwoh shows activity in rabbits that received a free or toxoid conjugated peptide relative to that in control rabbits that received saline. Figure 2 provides no data for a mammal that has been administered a whole, non-endogenous CETP. Further, the peptide vaccine of Kwoh are not reported to provide a blood plasma condition in which the level of CETP activity in a mammal falls below 20% of the level found in the untreated mammal.

Appellant's arguments have been fully considered but are not found to be persuasive. Although the data from Figure 2 of Kwoh do not show rabbits receive whole non-endogenous CETP, the 96/39168 publication teaches a method of modulating the endogenous active cholesteryl ester transfer protein (CETP) in a mammal such as a rabbit comprising administering to said mammal a full-length human CETP of SEQ ID NO: 1 of WO 96/39168, or a taxoid conjugated human CETP peptide, which are non-endogenous CETP, in an amount effective to stimulate an immune response such as anti-CETP antibody wherein said antibody inhibits the function of CETP such as reducing the CETP activity compared to that of the untreated mammal (See abstract, summary of invention, claim 2 of WO96/39168, Figure 2, in particular). Given that the non-endogenous CETP peptide increases HDL cholesterol while decreases CETP activity as operable embodiment as taught by the WO96/39168 publication, one skilled in the art at the time the invention was made would have envisaged the whole non-endogenous CETP would also carries out the same function as that of the peptide fragment. While the reference is silent that the reference method reduces CETP activity below 20% of that of the untreated mammal, the reference method inherently would achieve the same results given that the reference non-endogenous CETP (abstract, summary of invention and claim 2 of WO 96/39168 publication) is the same as that of the claimed non-endogenous CETP; the reference mammal (animal model) such as the New Zealand white rabbit is the same mammal as disclsoed on page 16 lines 30 of

instant application; the reference method steps such as the animals were boosted twice at one month intervals is the same as instant application (see page 17, line 15-16 of instant specification). The autoantibodies generated from the same non-endogenous CETP in the mammal inherently has the same functions, such as increasing HDL cholesterol, decreasing CETP activity as taught by the WO96/39168 publication. Therefore the claimed method appears to be the same as the prior art method. Since the Patent Office does not have the facilities for examining and comparing the method of the instant invention to those of the prior art, the burden is on applicant to show that the prior art method is different from the claimed method. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977).

At page 21 last paragraph of the Brief, Appellants argue that Table 1 on page 11 of Kwoh only provides data from example 2 in which rabbits were administered a free peptide or a toxoid-conjugated peptide vaccine. Table 1 does not even have one example of achieving the low level of LDL-cholesterol achieved by Appellants' method.

Appellant's arguments have been fully considered but are not found to be persuasive. The 96/39168 publication teaches administering whole non-endogenous CETP for a method of modulating the level of endogenous cholesteryl esteryl transfer protein (CETP) activity (See abstract, summary of invention, claim 2 of WO96/39168, Figure 2, in particular). The 96/39168 publication further teaches administering non-endogenous CETP peptide and toxoid conjugated CETP peptide as pointed out by Appellants. In fact, the instant specification discloses administering human CETP peptide to rabbit, using the same animal model (See page 17, lines 2-3 of instant specification). Although Table 1 of the reference does not have example of achieving the low level of LDL-cholesterol achieved by Appellants' method, given that the non-endogenous CETP peptide increases HDL cholesterol while decreases CETP activity as operable embodiment as taught by the WO96/39168 publication (abstract, Figure 2, in particular), one skilled in the art at the time the invention was made would have envisaged the whole non-endogenous CETP would also carries out the same function as that of the peptide fragment.

While the reference is silent that the reference method reduces the level of LDL-cholesterol to less than 10% of the total cholesterol, the reference method inherently would achieve the same results given that the reference non-endogenous CETP (abstract, summary of invention and claim 2 of WO 96/39168 publication) is the same as that of the claimed non-endogenous CETP; the reference mammal (animal model) such as the New Zealand white rabbit

is the same mammal as disclsoed on page 16 lines 30 of instant application; the reference method steps such as the animals were boosted twice at one month intervals is the same as instant application (see page 17, line 15-16 of instant specification). The autoantibody generated from the same non-endogenous CETP in the mammal inherently has the same functions, such as increasing HDL cholesterol, decreasing CETP activity as taught by the WO96/39168 publication. Therefore the claimed method appears to be the same as the prior art method. Since the Patent Office does not have the facilities for examining and comparing the method of the instant invention to those of the prior art, the burden is on applicant to show that the prior art method is different from the claimed method. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977).

At page 22 of the Brief, Appellants argue that the claimed invention calls for achieving a maximum value of 10% for LDL-cholesterol, showing data where LDL-cholesterol is essentially completely eliminated. The Kwoh reference does not meet or suggest the teaching, "less than 10%", completely aside from the fact that the methods compared are different. From consideration of Kwoh, the description of the peptides in Examples 1 and 2 of Kwoh clearly distinguishes the Kwoh teachings from the recitations of Appellant's claims. The person of ordinary skill in the art is not informed that reduction of LDL-cholesterol to a level of less than 10% is possible to achieve.

Appellant's arguments have been fully considered but are not found to be persuasive. The 96/39168 publication teaches administering whole non-endogenous CETP for a method of modulating the level of endogenous cholesteryl esteryl transfer protein (CETP) activity (See abstract, summary of invention, claim 2 of WO96/39168, Figure 2, in particular). The 96/39168 publication further teaches administering non-endogenous CETP peptide and toxoid conjugated CETP peptide. Given that the non-endogenous CETP peptide increases HDL cholesterol while decreases CETP activity as operable embodiment as taught by the WO96/39168 publication, one skilled in the art at the time the invention was made would have envisaged the whole non-endogenous CETP would also carries out the same function as that of the peptide fragment. While the reference is silent that the reference method achieving a maximum value of 10% for LDL-cholesterol, the reference method inherently would achieve the same results given that the reference non-endogenous CETP (abstract, summary of invention and claim 2 of WO 96/39168 publication) is the same as that of the claimed non-endogenous CETP; the reference mammal (animal model) such as the New Zealand white rabbit is the same mammal as disclsoed on page

16 lines 30 of instant application; the reference method steps such as the animals were boosted twice at one month intervals is the same as instant application (see page 17, line 15-16 of instant specification). The autoantibody generated from the same non-endogenous CETP in the mammal inherently has the same functions, such as increasing HDL cholesterol, decreasing CETP activity as taught by the WO96/39168 publication. Therefore the claimed method appears to be the same as the prior art method.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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